Title: Breast and colorectal cancer risk in monoallelic *MUTYH* carriers ascertained via multigene panel testing

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Whether monoallelic *MUTYH* mutation carriers are at increased risk of breast cancer (BC) and/or colorectal cancer (CRC) remains controversial. We aimed to determine whether monoallelic *MUTYH* mutations are associated with increased BC and/or CRC risk by comparing the frequency of *MUTYH* mutations among BC and CRC cases to controls from a multi-gene panel testing (MGPT) cohort.

Cases included Caucasian individuals with female BC (N=16,867) or CRC (N=2,571) who had MGPT including *MUTYH* at a clinical diagnostic laboratory. Control cohorts for the BC (N=10,854) and CRC (N=27,439) comparisons included Caucasian individuals who had MGPT including *MUTYH* at the same laboratory without personal history of BC or CRC, respectively.

Frequencies of the two most common *MUTYH* founder mutations, p.G396D and p.Y179C, were assessed independently as well as combined. Odds ratios (OR) were obtained from logistic regression analyses after adjusting for covariates.

No association was found between female BC and carrier status of p.G396D alone (OR=0.9, 95% CI=0.7-1.1, p=0.26), p.Y179C alone (OR=0.9, 95% CI=0.6-1.4, p=0.69) or both mutations combined (OR=0.9, 95% CI=0.8-1.1, p=0.24) after controlling for personal and family history of CRC and carrier status of mutations in other genes. Similarly, no association was found between CRC and carrier status of p.G396D alone (OR=1.2, 95% CI=0.8-1.7, p=0.33), p.Y179C alone (OR=0.7, 95% CI=0.3-1.4, p=0.31) or both mutations combined (OR=1.1, 95% CI=0.8, 1.4, p=0.72) after controlling for personal and family history of female BC and carrier status of mutations in other genes.

In summary, these data do not support a significant association of BC or CRC risk with monoallelic *MUTYH* carrier status. To our knowledge, this is the largest BC cohort used to assess BC risks among *MUTYH* monoallelic carriers and the first study to assess cancer association in *MUTYH* carriers identified on MGPT. Additional studies that include other *MUTYH* mutations, in addition to having larger CRC cohorts, are needed to confirm these results.

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